RIBBERT ON THE ORIGIN OF TUMORS.[1]

THE question of the cause of tumors is still unsolved. None of the theories thus far advanced has received general recognition. Many are of the opinion that the genesis of the various sorts of tumors must not be regarded as the same. In considering this question, and grouping all tumors under one head, it is not necessary to recite the various generally known theories concerning their origin. As the theory of Cohnheim has a direct bearing upon the ideas which are to be advanced, it may be briefly referred to. Cohnheim regarded as the cause of the formation of tumors a failure or irregularity in the embryonal tissues. He showed that in the course of normal development, and indeed in a very early period, certain groups of cells—either because they were superfluous, or because they were detached and separated from their normal connections, or from some other reason—did not continue to grow and build up tissue and organs, but lay in a latent state, and later developed into tumors.

As a foundation for his theory he pointed to the tumors, such as teratomata and dermoids, which are to be traced for their origin to such separated cells. He also called attention to the not seldom inheritance of tumors and their congenital existence. He emphasized the fact that many varieties of tumor were found only in certain particular locations, as the dermoids, and that others, as the myoma of the prostate and the rhabdomyoma of the uro-genital tract, are found where especially complicated developmental processes take place; and that carcinoma shows an especial predilection for the *ostia*, which is easily explained by the theory of separated cells. He called attention to the multiplicity of many new growths, as the uterus-myoma, which develops so often because in the uterus there is such rich material present that under certain physiological conditions it takes on an active growth; and which probably without the physiological excitement would not take on an abnormal growth and develop into tumors.

[1] Deutsche medicinische Wochenschrift, 1895, Nos. 1, 2, 3, and 4.

These are the most important of the grounds upon which the theory of Cohnheim is based. It is not necessary to go further into the details, excepting to say that when there comes to these quiet cells, after a longer or shorter time, an increased blood-supply or a diminution of the resisting power of the surrounding tissue or some other condition, they begin to grow and form a tumor.

This theory has been much contested. It had and has as many champions as antagonists. Among the latter is Von Zenker, who declared before the *Naturforscher-Versammlung* in Berlin, in 1886, that the theory in general was not only improbable but impossible, and especially in regard to the carcinomata. Weigert declared that Cohnheim himself had subsequently retracted his opinions concerning the genesis of tumors.

An important obstacle has always remained in the way, and that is that these hypothetical separated cells cannot be discovered. This leaves but little actual data upon which to base a theory, and moreover the actual discovering of such must needs be very difficult. It has been the fortune of Roux[1] to discover separated colonies of cells in the middle, more rarely in the inner embryonal layer of frog embryos, sometimes in large numbers, once as many as thirteen, scattered among the other cells. He was able to tell the conditions under which these cells developed. Late impregnation is the most important. Roux's observations are, of course, not complete, for he could not say what would become of these cells, and whether a tumor would have developed from each one. They taught, however, the possibility of a separation of cells, as Cohnheim had assumed.

Of no less interest are the observations of Barfurth,[2] who observed in his experiments in the regeneration of the embryonal layers that by puncturing and turning in the ectoderm of the gastrulæ that a growth of cells very like a dermoid took place. Here also we do not know what such a group of cells would do in a fully-developed embryo.

[1] Virchow's Archiv, Band CXIV, und Verhandlungen der Naturforscher-Versammlung in Wien, Sitzung der Section für pathologische Anatomie, am 26. September, 1894.

[2] Anatomische Hefte, I. Abtheil, Heft IX.

The observations of Roux and Barfurth, though very interesting and important, have thrown no light upon what might be the condition of such cells when the animal reached its complete development.

The older experiments with the experimental depositing of tissues have been without result. Tumors could not be made to grow from bits of all the different kinds of tissue which were implanted in the parenchyma of organs, in the blood-vessels, and in the anterior chamber of the eye. Nor were these experiments with any better results when, as Zahn and Leopold suggested, bits of embryonal tissue were used. Sometimes in the beginning there was a slight growth of the new tissue, but it always resulted in atrophy and absorption. The real cause of this was in all probability due to the fact that the new tissue was transferred to another animal body in which it encountered new and unusual vital conditions. When we consider that the actively developing bacteria are sensitive to transfer to a new animal body, that carcinoma which is of very active growth has only rarely been transplanted to an animal of the same species, and that deep transplanted tissue has always become absorbed, it is not difficult to conceive that these experiments with fœtal tissue should give so little result.

Though experimental investigations have given no considerable support to the theory of Cohnheim, still the best explanation that we have had of the origin of certain tumors has been from this hypothesis. This is especially true of the dermoid tumors and the rhabdomyoma. As a common example is the discovery by Grawitz,[1] of the tumors developing from separated bits of the suprarenal bodies. This discovery has a very important bearing upon the development of tumors from displaced embryonal cells, and will be spoken of later. For the present it suffices to observe that in connection with "separations" from the suprarenal bodies the development of malignant tumors is relatively frequent. But the presence of bits of suprarenal bodies underneath the capsule of the kidney is no rare condition, and, indeed, much more frequent than is the development of new growths

[1] Virchow's Archiv, Band XCIII.

from such separated bits of tissue. The same is true of the small masses of the same organ sometimes found in the broad ligament, in the epididymis, and in the liver. Most of these separations never go on to abnormal growths.

In many other cases, the separation of a small part of an organ which is otherwise normal does not result in the formation of a tumor. As examples may be cited the accessory thyroids, which might develop into tumors, but which usually remain unobserved; the accessory spleens, which show no more abnormality than the chief organ; and the accessory livers.

Why does no tumor develop in these cases? The reason is that the accessory part is constructed like the main organ from which it sprang, and that it can functionate quite as well as that. There is no special reason why these small bodies should give rise to tumors. When tumors do develop from them it is necessary to seek for some special explanation for such occurrences.

How is it then to be explained that tumors develop from fœtal "separations"? It must be borne in mind that the "separations" do not represent entire sections of the organ which contain all the elements of the organ in typical arrangement, but are composed of but a few single cells or cell-groups. This may be more fully elucidated.

The development of an organ follows through auto-differentiation existing as an inherited quality in the cells. Naturally this differentiation can only go on regularly when the cells, from the very beginning of their development, can develop one after another in a closed series. Each cell then places itself in typical arrangement in the organic whole. Assuming that one or more cells, without becoming deprived of any of their nourishment or injured in their growth, become partially or completely separated from their normal connections, the result is that their typical development is done with. Their further progress depends upon whether they still remain in more or less connection with the mother tissue or are entirely separated. The size and general character of the "separation development" will vary, depending upon whether the structure is the same as that of the orig-

inal organ, or whether there is a greater or lesser deviation from the parent structure, even to an entirely atypical growth. Depending upon these differences is the duration of the proliferation.

The normal organ grows until its completion,—*i.e.*, until it reaches its inherited size. At that time, all of its parts have been developed; and when this point has been reached, a further increase in its cells is prevented. By the size or tension of the organ, which is an inherited factor, is understood not alone the complementary mechanical pressure of the cells, but the sum of all of the complementary influences of the organ one upon another.

Such a point of tension is reached in the accessory bodies when they repeat the structure of the original organ. Then after a time the growth will stop.

The greater the deviation from the normal structure, the less will the further growth be checked by this cellular tension and just so much longer will the proliferation continue. If the development is a completely atypical one, a cessation of cell proliferation never really takes place. Thus arise the malignant tumors.

The cast-off cell-group need not take up any especial room; they can exist within the substance of the organ. Such conditions need not always lead to the formation of tumors. If the separated cells have a feeble vitality, or do not find sufficient nourishment in their new location, or are surrounded by too great resistance, they may perish. If the conditions of intrinsic growth and extrinsic resistance are exactly balanced, they may lie quietly for a longer or shorter time till one or the other of the conditions becomes changed. Such a condition would not often occur, but the separated cells usually go on developing and proliferating. The tumors which have their origin in such cells very rarely, therefore, begin from unchanged cells which have lain dormant for a long time, but must be regarded as continuations of a growth begun in fœtal life, and which has become accelerated as the conditions for growth became more favorable.

Ribbert assumes that the origin of tumors from "separated cells" does not depend on the embryonal character of the cells, but upon

their separation from their organic connections. So long as the cells continue to grow under the laws which govern the normal development of the organ their growth is a typical one; but when they become partially or completely separated from these conditions, they may form tissue which resembles more or less closely the structure of the organ, or it may be entirely different; as the embryonal character of the erring cells is not a matter of consequence, these cells can go on to the development of tumors immediately after birth. A consideration of the tumors which arise from abnormal processes in the development of the fœtus is next in order.

The least questioned of these are the remains of fœtal cavities and canals which have become abnormally enlarged. To this group belong the embryonal fistulæ and ducts of embryonal cysts, and the cavities which have their origin in the ductus thyroglossus.[1] To this class also belongs the cystic formation in the navel due to a partial patency of the ductus omphalomesentericus and designated as enterocystoma, and also the hydatids of Morgagni, and the cavities which originate in the remains of the ducts of Gartner.

Next come the external dermoid cysts which are due to inclusions of parts of the epidermis, and which Chiari taught remained connected with the superficial epithelium.[2] The fissural position of the dermoids—that is, their presence in places where fœtal fissures had existed or where clefts were closed, and because of which such inclusions might naturally occur—supports such a conclusion. The dermoids inside of the body, in the abdomen, lungs, etc., must be explained by a complete separation of the epithelial elements from which they take their rise. Cysts with ciliated epithelium, of which Hess[3] has recently reported such a cyst occurring on the hand, are explained on the ground of fœtal implantation.

Cholesteatoma of the cranial cavity cannot be classed with the dermoids. This tumor is regarded by many as a development and

[1] Haeckel, Archiv für klinische Chirurgie, Band XLVIII.

[2] Zietschrift für Heilkunde, Band XII.

[3] Zeigler's Beiträge, Band VIII.

metamorphosis of the endothelium of the pia, though most observers are now inclined to believe that it originates in epithelial cells which have some way become deposited in the cranial cavity. Ribbert[1] has examined a case in which there was nothing to indicate that the three-layered epithelial coat of the inner surface of the cholesteatoma had any connection with the endothelium of the pia. The very sharp line of demarcation between the epithelium and the normal pia mater made the idea of the origin of the tumor from "separated" epithelial cells seem very probable. This idea has a strong support in the case described by Bonorden,[2] in which the tumor contained glands and hair-follicles, structures belonging only to the external skin.

It must be assumed from the above observations that both the dermoids and cholesteatomata have their origin in groups of cells which have become turned in from the outer embryonic layer, which is indisputably the case with the former class of tumors. Ribbert goes further and assumes that not only epithelium, but also connective tissue can be thus dislocated, so that on the one side these cells can be well nourished and on the other side preserve an intact and permanent epithelial surface. In no other way can it be explained why the epidermis retains its typical form and does not simply build up a pile of disorderly epithelial cells. The same is true of the cholesteatoma of the ear, as it occurs as a primary growth in the cavities of the petrous bone. As is the case with the superficial dermoids, this tumor often remains in close connection with or very near the primary tissue. Later on it can happen that by virtue of the growth of the body and mobility of the organs the growth becomes separated from its origin. This same process of separation can also take place in the peritoneal epithelium. Ribbert has observed multiple cysts on the surface of the spleen lined with such epithelium.[3]

Next in order in the cystic epithelial structures come the tumors which arise from the glandular or adenomatous structures.

[1] Dissertation von Haegi, Ueber zwei Fälle von Cholesteatomen der Hirnhäute, Zürich, 1894.

[2] Ziegler's Beiträge, Band XI.

[3] Vide Dissertation, by Reuggli, Multiple Cysten der Milz, Zürich, 1894.

The thyroid is an organ which here comes into special consideration. The presence of accessory lobes to this organ is well known. Most of these, as above stated, show no tendency to abnormal growth. They do often become enlarged to a considerable size. The observations of Ziemssen are important, which show that these accessory nodules may occur within the trachea and be the origin of intratracheal adenomata.[1] Bruns states that such separations occur which he is entirely unable to explain upon histogenetic grounds.[2] Radestock[3] declared that he had been unable to find any connection between these intratracheal growths and the thyroid gland. Paultauf[4] came to the conclusion that the deposit was not an embryonal one, but that a direct growth of the thyroid through the tracheal wall took place on the ground of a probably fœtal connection of the thyroid with the trachea. He was able to discover the direct connection between the two. He also asserted that when deposits of tissue were of an embryonal character an active growth should be expected. The fact that most of the accessory thyroids show no great tendency to enlarge contradicts Paultauf's theory. A fœtal "separation" must have a certain cause, and this cause can be assigned not only to the "separation," but to the subsequent abnormal proliferation of the cells. Though there remain a connection between the superficial dermoids and the skin, the internal dermoids, though they have no epithelial connections, are of an analogous type.

It may be observed here that the "separation" of a bit of tissue must not be regarded as a passive process, but that, according to Cohnheim, an active and excessive growth of some tissue into another favors its becoming eventually included in the other and possibly entirely separated from its original attachments.

The thyroid may be used to illustrate in still another direction.

[1] Ziemssen, Handbuch der speciallen Pathologie und Therapie, Band IV.

[2] Bruns, Beiträge zur klinische Chirurgie, Band II; Heise, Ueber Schilddrüsentumoren im Innern der Trachea, Edenda.

[3] Ziegler's Beiträge, Band III, S. 291.

[4] Ziegler's Beiträge, Band XI, S. 71.

Wölfler[1] has endeavored to demonstrate the development of goitre from "fœtal adenomata,"—that is, from groups of thyroid cells which did not take part in the normal growth of the organ, but remained undeveloped. This idea has been contested by Hitzig,[2] who claimed that the anatomical findings do not corroborate Wölfler's idea, but that the growth seems to proceed out of the normal structure of the gland.

A second gland from which aberrant portions may go on to the formation of tumors is the mamma. Most commonly these are adenomata. E. Martin[3] has observed an interesting case. A lobule became separated from a supernumerary mamma, and converted into a fibro-adenoma. It still remained connected with the supernumerary gland by a very narrow string of tissue.

The adenomata which occur in the liver are evidently due to disturbances of the embryonal development. Ribbert has observed such a case, in which, in a fourteen-year-old boy, the organ presented very marked changes without any outward signs except a slight venous obstruction. The organ contained numerous nodules, varying in size from that of a pin-head to a pea, and corresponding in color with the rest of the liver. Microscopically, they differed in structure from the rest of the gland in that the strings of cells were much broader. Transverse section of these strings show that instead of one or two cells, they represented a thickness of four or five cells, so that, with the exception of a lumen, they resembled gland tubules.

In the cases of the above adenomata, certain parts of the glandular structure failed to develop into gland substance. Here, as in the dermoids, it must be borne in mind that not only the epithelium but the underlying connective tissue as well is concerned in the process. When this also develops into tumor tissue the result is fibro-adenoma or fibroma. Tumors of pure connective tissue may thus develop independently of the glandular tissue.

[1] Ueber den Entwickelung und Bau des Kropfes, Langenbeck's Archiv, Band XXIX.

[2] Archiv für klinische Chirurgie, Band XLVII, Heft 2.

[3] Langenbeck's Archiv, Band XLIV, Heft 4.

A tumor without the epidermis formation of the dermoid or the follicles of adenoma may result from these conditions. In such a tumor there would be a connective-tissue mass containing scattered epithelial cells having no glandular arrangement, but simply scattered about in disorderly groups. Whether such growths occur in the embryo we do not know. Cohnheim's original idea was that carcinoma had its origin in this manner. This sort of misdevelopment occurs in the jaw, and gives rise to abnormal formation of the teeth. It has been designated by Malassez [1] as *débris paradentaires*. It presents chains of epithelial cells which, in the formation of the parts, did not come into play but which still persisted. From these structures superfluous teeth,[2] cysts and adenomatous-like structures,[3] and sometimes, though rarely, carcinoma may develop.[4] Whether carcinoma really does arise from such structures or whether different conditions are superadded is still a question. The same may be said of the so-called branchiogenous carcinoma which occurs in the remains of the branchial clefts.[5] Here, too, it cannot be said whether the carcinoma has its origin from simple epithelial clumps or whether it springs secondarily from the epithelium of embryonic fistulæ or cysts.

So far tumors of epithelium have been considered. When we turn to the tumors of the connective-tissue type, we first come to two tumors described by Chiari [6] which are related to the dermoids, as he has seen fit to designate them as "fissurale," but which are formed not only out of epithelium, but also hair-follicles, glands, connective tissue, and fat. There are the tumors found on the raphé perenei of the new-born. Chiari accounted for them by assuming an excess of

[1] Archives de Physiologie normal et pathologique, 1885.

[2] Hildebrand, Deutsche Zeitschrift für Chirurgie, Band XXXV.

[3] Krause, Virchow's Archiv, Band CXXIV; Becker, Archiv für klinische Chirurgie, Band XLVII; Derujinsky, Wiener klinische Wochenschrift, 1890, No. 40; Chibret, Archives de Médecine expérimentale, 1892, No. 2; Massin, Virchow's Archiv, Band CXXXVI, S. 328.

[4] Ziegler, Lehrbuch, II Hälft, S. 486 (nach Bruns).

[5] Bruns, Mittheilungen aus der Chirurgischen Klinik zu Tübingen, 1884.

[6] Prager medicinische Wochenschrift, 1889, No. 49.

formative material, which was not used at the coalescence of the lateral gluteal masses.

Probably other congenital fibrous tumors in other locations are of analogous origin.

Tumors containing cartilage, which are frequently found in other parts of the body, are good examples of fœtal deposits. They are rarely composed entirely of cartilage, but are much more frequently made up of two or more kinds of tissue. Leaving out of consideration the cartilaginous tumors connected with the osseous system, the origin of these tumors has been sought for in "separated" cells and in a metaplasy of pre-existing tissue. As to the latter, it must not be lost sight of that a metaplasy of the tissues of the organ containing the tumor has never been observed; but that the metaplasy only occurs from the remaining portions of the new growth,—that is, from elements which are really "separated" cells, and which are then to be regarded as the primary embryonal stage in the development of the cartilage. Naturally all of these tumors are characterized by some peculiar features in the development of such cartilage from fœtal aberrant cells. They invariably grow in locations and in organs which, in their developmental stage, were near to tissue normally containing cartilage, or in which cartilage had grown from aberrant cells. Many of these tumors, on every side, present the evidences of such origin.

In the neck small cartilaginous subcutaneous tumors sometimes occur which are undoubtedly remains of the embryonal arches.[1] The chondroma of the parotid evidently originates from the "separated" cells of the embryonal arch or from the ear cartilage. Cartilaginous islands and tumors containing cartilage have also been observed in the thyroid, which are of the same character.[2] The carti-

[1] Buttersack, Virchow's Archiv, Band CVI, S. 206; Samter, Ibid., Band CXII, S. 77; Zahn, Ibid, Band CXV; Hoffmann, Greifswalder medicinische Verhandlungen, VI, February, 1892; Grimm, Prager medicinische Wochenschrift, 1892, No. 10.

[2] Zahn, Deutsche Zeitschrift für Chirurgie, 1885, Band XXII; Recklinghausen, Deutsche medicinische Wochenschrift, 1892, S. 339.

laginous tumors of the buccal cavity and the hairy polyps of the throat are, according to Arnold,[1] due to abnormal developments in the formation of the arches of the mouth. Ribbert[2] has seen in a new-born child a tumor of the lower lip composed of cartilage, connective tissue, fat, and teeth, which could only be accounted for by an aberration of cells in the formation of the lower jaw. He has also seen a tumor of the upper lip which contained cartilage and which could only be accounted for by an analogous process. The rare chondromata of the mamma gets its cartilage, according to Leser,[3] from the underlying ribs. Coën thinks that it is due to metaplasy. In the enchondromatous tumors of the genito-urinary organs, especially the testicle and kidney, the cartilage might come from the spinal column.

The so-called ecchondrosis physalifora of Virchow[4] belongs to the chondromata. Virchow explained this tumor by a growth and mucoid metamorphosis of remains of the spheno-occipital cartilage, after Heinrich Müller had stated that he thought it originated in remains of the chord. Pathological anatomists are divided on this question; some siding with Virchow, others with Müller.[5] Among the latter is B. Klebs.[6] Under the direction of Ribbert, Steiner[7] has made some original investigations in this line. He was able to confirm Müller's theory. The jelly tumors are the result of developmental abnormalities. Whether or no a cell "separation" plays any *rôle* is a question. It is very probable that it does, for these tumors are always situated directly underneath the dura of the clivus, while the remains of the chord are always found centrally in the cartilage or bone-furrow. Klebs recognized the possibility of misplacement

[1] Virchow's Archiv, Band III.

[2] Schoch, Dissertation über einen Congenitalen Zahnhaltigen Tumor der Unterlippe, Zürich, 1893.

[3] Ziegler's Beiträge, Band II, S. 381.

[4] Virchow, Die krankhaften Geschwülste.

[5] Zeitschrift für rationelle Medicin, 1858.

[6] Allgemeine Pathologie, 1889, Band II.

[7] Centralblatt für pathologische Anatomie, 1894, No. 11.

of the chorda, on the ground of having found this condition in an embryo with spina bifida. Hirschberg[1] has described two good-sized retropharyngeal tumors which, on account of their histological structure, he regarded as products of chorda remains.

Embryonal developmental disturbances come into consideration in the genesis of the osteomata which arise from chondromata. It is well recognized that many of the exostoses are due to abnormal intra-uterine processes; and there is a pretty well-grounded belief that the paraosteal bony tumors,—that is, those which do not arise from bone,—occurring in myositis ossificans progressiva, are to be accounted for by a deposit of periosteum-cells in the muscles and tendons. The rare osteoma cerebri is probably due to an embryonal misplacement of bone-producing cells. Multiple osteomata of the trachea may be placed with this same class. Here are found numerous small bony prominences of the mucous membrane, usually in close connection with the tracheal wall, and which are usually regarded as ossified enchondroses or as exostoses of the cartilage rings. Ribbert[2] has seen two cases in which these little osteomata were not all in bony or cartilaginous connection with the tracheal rings, but many of them appeared as separate bodies or connected with cartilaginous islands in the submucous connective tissue, scattered about and distributed along in irregular rows. He is of the opinion that in the embryo an abnormal outgrowth of the tissues which go to make up the tracheal rings takes place, whereby some of this tissue becomes deposited in the mucous membrane. From this tissue, cartilage develops which eventually becomes converted into bone.

Pronounced examples of fœtal aberration are found in many forms of lipomata. First of all are the fatty tumors which grow in the spinal canal in spina bifida, and which have been described by Von Recklinghausen.[3] Ribbert has observed the same thing;[4] and Arnold[5]

[1] Loc. cit., p. 310.

[2] Dissertation of Mischaikoff, Ueber Knochenbildung in der Trachealschleimhaut, Zürich, 1894.

[3] Virchow's Archiv, Band CV.

[4] Ibid., Band CXXXII.

[5] Ziegler s Beiträge, Band XVI.

has reported a similar case. Not only is fatty tissue found, but also connective tissue, muscle, and glandular tissue as well.

Deposits of foreign cells occur also in the skull at the site of fœtal clefts. Mixed lipomata are found in the cranium; and it is possible that the pure lipoma cerebri originates from aberrant cells. To this class belongs the congenital pharyngeal polypus, which is composed almost entirely of fatty tissue.

Rhabdomyoma belongs in this class. It occurs most commonly in the uro-genital tract. Ribbert[1] tried the experiment of making striped muscular tissue develop by metaplasy from the unstriped tissue, but has had to conclude that each of these varieties of muscular tumors must develop from independent cells, which it is very easy to conceive are the result of fœtal aberrations, and which in the uro-genital tract is not a difficult thing to believe. As to the kidneys, which are developed from two different genital layers, it is very easy to understand, as Hanan has shown, how foreign embryonal cells can become therein included. He endeavored to explain on this ground the cause of the rhabdomyoma found by Ribbert on the outside of the pelvis of the kidney. These tumors are much more seldom in other parts of the body. Wolfensberger[2] reported a rhabdomyoma of the œsophagus, and assumed that it originated from aberrant cells. Even the rhabdomyomata which occur in locations where nothing but striped muscle grows are probably also due to such fœtal aberrations. Corroborative of this view is the pronounced embryonal character of the new tissue of all tumors. The same is the case with rhabdomyoma of the heart as described by Kolisko.[3]

Whether or not leiomyoma has the same origin must still be further investigated. With the myoma uteri there is a possibility that the cause may be the same as that of the other tumors above discussed, but certainly in another sense from that of Cohnheim. The most recent observations of Hauser[4] would indicate that the remains

[1] Virchow's Archiv, Band CVI und CXXX.

[2] Ueber ein Rhabdomyom der Speisröhre, Ziegler's Beiträge, Band XV.

[3] Wiener medicinische Wochenschrift, 1893, No. 10.

[4] Münchener medicinische Wochenschrift, 1893, No. 10.

of the Wolffian ducts have something to do with causing the surrounding muscular tissue to develop into myomata. Babes, Diesterweg, Schroeder, and Ruge are of the same opinion; and Brens[1] and Von Recklinghausen[2] are very firm supporters of the theory. These observers have found inside of myomata epithelial cell collections in the form of cavities, canals, and cysts; a few containing ciliated epithelium. These structures need not necessarily have come from Wolffian bodies; they might, as Hauser has suggested, be derivatives from the uterine mucous membrane. Ribbert has a specimen in which a chain of epithelial cells extends seven or eight millimetres into the uterine wall, and which in the section appear as isolated epithelial islands. The extreme tip of this chain lies against a small myoma, but does not penetrate into its substance. Schottländer has seen the same thing, and claims that parts of the mucous membrane had grown into the tumor.[3] Hauser infers that the epithelial inclusion justifies assuming a similar abnormality of the musculature. That, of course, does not concern the Wolffian ducts. From this it may be concluded that the development of tumors can be so intimately associated with these epithelial collections that, as the uterus grows, these structures are dragged into the substance of the organ and their proliferation encouraged. In this abnormal process of dragging epithelial structures into the wall of the uterus, not only may this occur with the uterine glands, but simple islands of mucous membrane have been found deep within the uterine wall. Ribbert has discovered such an island lying along-side of a myoma, and in another case the epithelial cells penetrated the tumor.

Another tumor in which fœtal aberrations play a *rôle* is the glioma. Stroebe[4] has reported a case in which the tumor contained numerous acini lined with cylindrical epithelium. He was of the opinion that it originated in a folding out of the ventricle, and that the growth of the tumor had gone on with the extruded subepithelial

[1] Ueber epithelfürende Cystenbildung im Uterusmyomen, Wien, 1894. Deutsche medicinische Wochenschrift, 1893, S. 825.

[3] Zeitschrift für Geburtshülfe, XXIII.

[4] Naturforscher-Versammlung in Wien, 1894, Section für pathologische Anatomie.

glia layer. Ziegler[1] takes the ground that the neuroglioma ganglionare is probably due to developmental abnormalities. Wintersteiner[2] places glioma of the retina in the same class, assuming that it arises from fœtal "separations" of cells of the retina.

Associated with glioma are the tumors which, because of their situation on nerves, have been designated as neuroma, but which are really only connective-tissue tumors on the nerves; also the multiple neurofibroma of Von Recklinghausen,[3] which is, from a genetic point of view, very similar to the pharyngeal neuroma of Bruns.[4] They are often congenital and hereditary. It may be assumed that during the development of the nerve a disturbance occurs somewhere, which perhaps causes an abnormal arrangement of the cells or a deposit of connective tissue in the nerve. Ziegler states in general "that the development of that particular part of the nervous system was pathological, and that the subsequent growth of a fibroma was thereon engrafted."[5] Goldmann[6] is of the opinion that the nerve-sheath to a greater or lesser extent remains in a sort of embryonal condition, which later goes on to tumor-formation. It is not improbable that this embryonal character of the nerve-sheath depends upon an abnormal arrangement of the tissues. Perhaps still further-reaching aberrations come into consideration. Garrè found a neuroma containing epithelial cavities, which he believed originated in inclusions from the central canal of the spinal cord.

In the list of the congenital tumors due to developmental abnormalities must also be included the angiomata, especially the teleangiectasies, which are classed in the category of "fissure" new growths.

Lastly come the sarcomata. With these also there are forms which can be traced to embryonal defects. This is especially true of melanosarcoma arising from pigmental warts of the skin. For a long

[1] Lehrbuch, Band I, S. 310.

[2] Wiener medicinische Wochenschrift, 1894, No. 27.

[3] Die multiplen Fibrome, Berlin, 1882.

[4] Beiträge zur klinische Chirurgie, Band VIII, Heft 1.

[5] Lehrbuch der pathologische Anatomie.

[6] Beiträge zur klinische Chirurgie, Band X.

time these have been attributed to embryonal developmental disturbances. Melanosarcoma of the eye also belongs to this class. Martin[1] has reported a case in which a pigmental sarcoma of the choroid was associated with a congenital melanosis of the sclerotic. He assumed that there was a pigment anomaly of the choroid, which was the origin of the growth.

Another such tumor is sarcoma of the vagina. Ahlfeld,[2] Kolisko,[3] Hauser,[4] and Pick[5] have all observed these tumors, especially in children, and have all agreed upon their congenital or fœtal character. This conclusion is strengthened by the fact that these tumors sometimes contain other tissue, such as striped muscle fibres and epithelial cells. This last fact brings up the sarcomatous mixed tumors, which are undoubtedly due to embryonal defects in development. As examples of these may be mentioned the chondrosarcoma of the parotid and testicle and the rhabdomyosarcoma of the uro-genital tract. Still further must be taken into account the combination of sarcoma and other varieties of tumor with the dermoid cysts. Such combinations were described by Virchow[6] as occurring in the anterior mediastinum, and in the ovary;[7] by Biermann[8] in the ovary; by Pinders[9] in the mediastinum; and by Jores[10] in the lung. Hausemann[11] has reported an adenomyosarcoma of the kidney, the structure of which resembled teratoma. Hildebrand[12] observed a cystic kidney with sarcomatous degeneration, the cause of which he assigned to an abnormal union of the cortical and the medullary substances.

[1] Virchow's Archiv, Band CXXXVIII, S. 111.

[2] Archiv für Gynäcologie, Band XVI.

[3] Wiener klinische Wochenschrift, 1889, S. 222.

[4] Virchow's Archiv, Band LXXXVIII.

[5] Archiv für Gynäcologie, Band XLVI.

[6] Virchow's Archiv, Band LIII.

[7] Ibid., Band LXXV.

[8] Prager medicinische Wochenschrift, 1885, No. 21.

[9] Ueber Dermoidcysten der vorderen Mediastinums, Dissertation, Bonn, 1887.

[10] Virchow's Archiv, CXXXIII, S. 66.

[11] Berliner klinische Wochenschrift, 1894, No. 31.

[12] Archiv für klinische Chirurgie, Band XXVIII.

It must be borne in mind that tumors which are due to embryonal abnormalities show a tendency to become sarcomatous. Garrè and Goldmann have spoken of this, and showed how that the multiple fibroneuromata tend to become sarcomatous. Chiari[1] saw a case of multiple exostosis, one of the bony tumors of which became sarcomatous. The new growth he found sprang from the marrow of the exostosis.

From the above observations, even if not all of them, are considered demonstrative, we can conclude that many tumors must be referred to embryonal disturbances of development. This hypothesis, as applied by Cohnheim to all tumors, cannot, according to Ribbert, be made to include all classes, such especially as the carcinomata.

Since the theory of Cohnheim cannot be accepted for all tumors, little, then, remains known as to the cause of tumors which have an extra-uterine origin. But inasmuch as this theory does hold good for certain growths of embryonal origin, it may be possible that conditions similar to these intra-uterine abnormalities may occur during the period of postfœtal growth, and thus produce tumors in the tissues of the adult just as the hypothesis of Cohnheim assumes that tumor-producing changes occur in the tissues of the embryo. Or are the extra-uterine tumors of an entirely different nature?

It is hard to believe that at the time of birth the genesis of tumors suddenly changes. This can only be reconciled by the view that during the folding-in of the embryonal layers "separations" of cells occur. But this does not imply that after birth a similar shutting-out of cells from their normal connections cannot take place. Ribbert claims that this does occur, and bases his theory thereon. He makes the following declaration:

In the adult, as well as in the embryo, cells and cell-groups become separated from their normal connections and without having their nourishment shut off, remain in a latent state, and then begin again to grow and develop into tumors.

It must first be decided whether the cells of the adult have suffi-

[1] Prager medicinische Wochenschrift, 1892, No. 35.

cient power to originate a tumor. As has been stated above, the growth of an organ ends when it reaches its inherited size and when a certain degree of tension is attained. There are two conditions under which a further proliferation may occur,—compensatory hypertrophy and regeneration. The first is caused by direct functional irritation of the secreting part of an organ, as in the kidney; or through the influence of the nervous system, as in the muscles and probably also the testicles. Regeneration replaces by new development tissues which have been destroyed. Sometimes, as in the skin, it is a continuous and permanent process; in other cases it takes place only under certain conditions. The cause of regeneration of destroyed tissues is an increase of the tissue tension. The only thing which can be observed is the manifestation of this slumbering cellular potentiality in the building-up of the destroyed tissue. If the cells could not proliferate, the tissue tension could not be accommodated. Thus the power of regeneration depends upon the capacity for proliferation of the cells. This varies greatly in the different organs. It is absent, for example, in cartilage; very slight in the liver; and very active in the salivary glands and skin. After H. E. Ziegler and Von Rath had demonstrated the fact that regeneration begins in the least differentiated cells of an organ, Ribbert found the same to be especially true of the salivary glands and the kidneys, in which regeneration takes place in the efferent ducts while the functional elements do not take any part.

Liver-cells, for example, which normally do not have to proliferate rapidly are capable of regenerating when the necessity arises. About a wound of the liver many cells are found to contain mitoses.

In the fully-developed adult body, cells which in the normal organ show no tendency to increase, are capable of proliferation. In many tissues, as the skin, this proliferation goes on as a normal function. The question naturally arises as to whether such cellular proliferations occur independent of regeneration and compensatory hypertrophy, and whether this proliferative tendency of cells in the adult body may not be the cause of tumors.

Ribbert is of the opinion that this is the case. If the diminution of the tissue tension is the exciting cause on the one hand; in the same sense, the separation of cells from this normal tissue connections is an exciting cause on the other. The restraining influence of the surrounding tissues ceases, and the latent power of the cells becomes manifest. In tissues where there is normally a constant proliferation of cells, as in the skin, the cell-proliferation does not tend to diminish the tissue tension, but rather increases it. As is the case in regeneration, different degrees of proliferative activity are manifested by different kinds of cells.

As in embryonal tissue, so it is here that the character of the new growth depends upon the character of the separated cells, and how much the new growth deviates from the structure of the parent tissue. The more pronounced the atypical character is, the less is the possibility of restoration of the normal growth-checking tension between the tissues, and just so much more lasting will the proliferation be.

A tumor need not develop in every case of cell-separation, but, as is the case in the embryo, the aberrant cells may perish, or by virtue of the surrounding resistance they may lie dormant for an indefinite period. But when the resistance of the tissues becomes reduced, a tumor develops. All of this goes to show that in adults the separation of living cells from their normal connection is the cause of the development of tumors.

As yet, it may be said, there is insufficient ground for assuming that such is the cause of tumors. More accurate histological study of this question will bring us still nearer to the truth. The commonest example of tumor originating in this way is the multiple chondromata and exostoses. Virchow[1] was the first to show that bits of cartilage which became separated from their connections with the rest of the cartilage by abnormal ossification of the epiphysis-lines in rachitis were the origin of enchondromata. This declaration met with general approval. Since then the same observer has made other similar

[1] Die Krankhaften Geschwülste, I, S. 478.

investigations, the last of which was published before the Naturforscher-Versammlung in Halle, at which time Ackermann and Hanan made similar reports. Ackermann found separated islands of cartilage in the case of a large enchondroma of the knee-joint region. Hanan found the same thing in a case of multiple chondromata of the skeleton. Later observations have been reported by Zeroni,[1] Colley,[2] and Nasse.[3] Some of these observations confirm the idea that not only chondroma but osteoma as well originates from such islands of cartilage. Of course, solitary as well as multiple tumors can develop in this way.

Of the connective-tissue tumors, sarcoma is the most important. Sarcoma often originates in other connective-tissue tumors. It often occurs at the seat of fractures, implying a "separation" of periosteal or marrow-cells. In the same line must be considerated the recently-studied development of sarcoma from decidua and placenta. These tumors have been designated as sarcoma deciduo-cellulare, deciduoma malignum, and sarcoma of the chorionic tufts. Gottschalk[4] has written upon this variety of sarcoma; so also have Klien[5] and Marchand.[6] The non-malignant tumors described by Zahn[7] and Kahlden[8] also belong here. In all of these cases the tumor originated in remains of the fœtal membranes or placenta from separated cell-groups.

Turning now to the epithelial tumors, the question arises as to whether growths similar to dermoid cysts and cholesteatomata can originate after birth. The answer is in the affirmative. We know that experimentally tumors similar to the dermoid growths can be developed. The experiments of Schweninger[9] and Kaufmann[10] show

[1] Arbeiten aus dem pathologischen Institut zu Göttingen, 1893.

[2] Deutsche Zeitschrift für Chirurgie, Band XXXVI.

[3] Berliner medicinische Gesellschrift, 25. Juli, 1894.

[4] Archiv für Gynäcologie, Band XLVI.

[5] Ibid., Band XLVII.

[6] Aerztlicher Verein in Marburg, 4. Juli, 1894.

[7] Virchow's Archiv, Band XCVI.

[8] Centralblatt für pathologische Anatomie, Band II, Nos. 1 and 2.

[9] Centralblatt für die medicinische Wissenschaften, 1881.

[10] Virchow's Archiv, Band XCVII.

that when bits of skin are buried in the tissues and covered by sewing the skin over them, cavities like dermoid cysts develop. Ribbert has modified the experiment by cutting out a skin flap which he introduced into the abdominal cavity, leaving it nourished by a pedicle, which was not severed. The connective-tissue surface of the flap grew fast to the peritoneum, thus enclosing the epithelial surface in a cavity. This cavity was found lined with epithelium, from which hair was growing, and filled with hair and exfoliated epithelial *débris*. The traumatic epithelial cysts which are observed most commonly on the fingers are analogous to the above. Here the callous skin forms the so-called "iris cysts."

According to many authors cholesteatomata occur in adults as a result of a similar process of displacement of cells. This is very probable in the tumors of the ear which are due to an ingrowth of epithelium from the defective tympanic membrane into the ear cavity and the neighboring bone-cells. Ribbert has been able to demonstrate the direct connection of the external epithelium with the lining of a cholesteatoma cavity. In such growths there is not only a growth of the epithelium, but also an active proliferation of the subepithelial connective tissue. This tissue is rich in cells and blood-vessels, and in it originate the giant cells which attack the bone. There is not only a change in the pre-existing tissue, but also, at least as far as the accessory cavities of the petrous and mastoid portions are concerned, an ingrowth of new connective tissue. On the other hand, Baginsky[1] explains the origin of cholesteatoma on the same ground as the above-mentioned tumors of the cranial cavity.

But little is known of the postembryonal displacement of gland structure which might give rise to adenoma. It is possible that adenoma of the liver belongs to this category. It occurs very commonly with cirrhosis of the liver, and is often, in such cases, regarded simply as compensatory hypertrophy. This may be right, so far as it corresponds in structure with the normal organ, leaving out of account the size and number of the cells. In other cases there is not

[1] Berliner klinische Wochenschrift, 1894, Nos. 26 and 27.

a great deviation from the normal appearance. May it not be concluded that portions of the hepatic tissue are separated from their normal relations and connections by the new growth of connective tissue, and grow independently and produce adenomata? The difference in structure would corroborate this view; and it is easy to understand that such isolated portions are not more capable of reproducing the normal structure of the liver.

In the same way can the true adenoma of the kidney be accounted for. In the ordinary contracted kidney are often found multiple small tumors, which differ more or less in their structure from the normal kidney. They are made up usually of irregular alveoli separated by septa and covered on their inner surface with projections. These structures can be abnormally formed uriniferous tubules, formed out of connection with the normal kidney structure. Ribbert has observed two tumors the size of a pin-head in the same kidney. In a connective-tissue wedge lying on the surface was found a small adenoma made up of a number of alveoli and separated entirely from the surrounding cortical substance.

Lastly, carcinoma may be considered. Here, too, are two questions to be decided: Can carcinoma arise from the "separation" of epithelial cells? and can we be sure upon the ground of anatomical observation that in the formation of carcinoma epithelial deposits really play a *rôle?* According to Ribbert's observations both of these questions can be answered in the affirmative. For the answering of the first question are two groups of facts. The first includes the observations of carcinomata which have developed after the removal of benign epithelial groups. The cases which have thus far been reported have all been ovarian cysts. Pfannenstiel[1] has worked up this subject, and says that many of the cases in the literature are imperfect, especially with regard to the histological examinations of the primary tumor, which were not thorough enough. The carcinoma developed either in the abdominal cavity or in the scar of the laparotomy wound. Pfannenstiel has reported one of the latter class. Several years after

[1] Zeitschrift für Geburtshülfe und Gynäcologie, Band XXVIII, Heft 2.

the removal of a small simple cystic ovarian tumor a typical adenocarcinoma developed in the abdominal scar. Pfannenstiel came to the same conclusion as Olshausen, that the development of the carcinoma was referable to the cystic tumor; that epithelial cells from the benign cystoma became detached and implanted either in the abdominal cavity or in the wound, and eventually developed into a carcinoma. He is of the opinion that the last process did not follow immediately upon the epithelial deposit, but that first an adenoma developed, and from that a carcinoma sprang. Ribbert is of the opinion that this is not the case, but that the epithelial cells undergo the same changes as when collections of such cells are placed in the peritoneum or in a wound. They tend to form a cyst as the epidermis cells do. They spread out over a surface and separate themselves from the connective tissue. A few cells become detached and easily enter the lymph-channels and form a carcinoma. In certain cases it cannot be denied that, as Pfannenstiel has assumed, an adenoma may precede the carcinoma.

In 1892, Professor Kröulein extirpated a tumor of the abdomen, which was found to be a monolocular cyst of the urachus, though at the operation its origin was not suspected, and which has been described in a dissertation by Dösseker.[1] Soon after the operation a very rapidly-growing carcinoma developed in the abdominal scar, and quickly caused the death of the patient. The large tumor-mass presented the typical picture of a carcinoma made up of soft protoplasmic cells. Ribbert observed that these cells enclosed an unusually large number of vacuoles, as he has observed only in the bladder, and previously described as peculiar to carcinoma of that organ.[2] It was upon this peculiar feature that he was able to declare that the cyst was a cyst of the urachus, and that some of its epithelium had become lodged in the abdominal wound at the operation. The tumor was not preceded by any cyst formation.

The second group of facts which come into consideration here

[1] Klinische Beiträge zur Lehre von den Urachus cysten, Zürich, 1892.

[2] Deutsche medicinische Wochenschrift, 1891, S. 1179.

contain the observations of metastases from benign adenomata. Struma of the thyroid belongs here. The observations of Cohnheim of metastases from a simple goitre are well known.[1] Von Recklinghausen[2] suggested that it might have been a "jelly" carcinoma. Since then a number of such cases has been reported, and the question has arisen as to whether goitre might not in some cases be really carcinomatous. The metastases alone bespeak the carcinomatous character of the tumor, while the observations of Marchand,[3] Middledorpf,[4] Von Eiselsberg,[5] and Ewald[6] have shown that the metastases have the simple structure of the ordinary soft goitre. This circumstance may seem to be contradictory to the theory of Ribbert. When no carcinoma develops, it may be said, this shows no tendency on the part of the aberrant cells to undergo carcinomatous degeneration. But it must not be lost sight of that there is an actual metastasis formation and uncircumscribed development of the epithelial cells originating in a benign struma. Whether or no the result is the formation of a typical histological picture of carcinoma is not of especial consequence as far as Ribbert's theory is concerned. It is important that the epithelium which becomes separated from its organic connections shows an exaggerated growth capacity. Here, as in the case of the above-mentioned ovarian cysts, the manner in which the aberrant epithelial cells grow is entirely dependent upon the circumstances which surround them in their new location.

The same is the case with adenomata of the liver. They show a tendency to metastasis, which tendency increases as the deviation from the normal structure of the liver is greater. Still, a tumor which nearly repeats the structure of the organ can give rise to these changes, as the case reported by Frohmann shows.[7] This formation of meta-

[1] Virchow's Archiv, Band LXVIII.

[2] Ibid., Band LXX.

[3] Aerztlicher Verein zu Marburg, 7. März, 1894.

[4] Archiv für klinische Chirurgie, Band XLVIII.

[5] Archiv für klinische Chirurgie, Band XLVI and XLVIII.

[6] Berliner klinische Wochenschrift, 1892, No. 37.

[7] Neuwerk's pathologisch-anatomische Mittheilungen, XVI.

stases is not to be wondered at when we think that these adenomata have been spoken of above as tumors, which develop disconnected from the general structure of the liver tissue, and in such an active manner that the vessels and lymphatics are easily encroached upon, —a condition which is easily possible in the liver.

In this connection may be mentioned a cyst adenoma of the testicle described by Adler. It was a simple cyst-adenoma without any suspicion of sarcomatous or carcinomatous degeneration. A year and a quarter later the patient died of cystic metastasis in the lungs. Similar to this are the cases of benign enchondroma which, by entering the veins, cause metastasis.

The two groups of metastasis-formation which have been briefly illustrated teach with much conclusiveness that epithelium from tumors which present the anatomical structure of benign growths, when it becomes dislodged from its organic connections can develop independently and give rise to tumors which correspond with the primary growth or to carcinomata.

This being conceded, it is not much of a step to declare that epithelium from normal tissue also, when in a similar manner it becomes separated, can develop in a similar manner and form carcinoma. It must be assumed that in such a case there is no checking of nutrition, or only for a short time, and that the conditions for development in the new location are favorable.

Certain objections to such a theory must naturally occur. It might be suggested that a separation of normal epithelial cells is hardly possible. In the analogous cases of the ovarian cysts and adenomata there was either an operative separation or the cells were in such an active state of development that the vessels were easily encroached upon and entered. In this light it is hardly to be regarded as accidental that adenoma forms metastases, which in the thyroid we refer to the lymphatic vessels and in the liver to the blood-vessels. All of these objections naturally are refuted when Ribbert has observed the splitting up of epithelial cells under such conditions, as will be shown. These observations were made, as we shall see, only in local metastases.

It is well known that cell-metastases occur without the formation of a tumor. This occurs in the separation of liver cells, bone-morrow cells, and placental giant cells. But whether these last two varieties of cells possess a more active developmental energy or not is a question. As to the liver-cells, it is certain that in the normal liver they very rarely present mitoses. It is evident, therefore, that the entrance of cells into the blood-current always occurs under abnormal conditions, and the latent developmental energy in such cells is usually not great enough to result in the formation of a tumor. Furthermore, these cell-separations occur under conditions of disease which usually result in the death of the patient, and which, therefore, do not favor an abnormal growth of cells.

If the power of proliferation in the metastatic cells is of influence upon the later development, we should expect, as is the case with carcinoma, a growth of the same; especially when of epithelial character, which would continue indefinitely to proliferate, as also occurs in benign epithelial tumors. It may be noted here that carcinoma in general originates almost always from epithelium in which mitoses are either always present or are present under certain conditions (as the mammæ). Such cells are those of the ducts of glands, the superficial epithelium of the skin and mucous membranes, the glands of the intestine and the testicle. Structures in which the epithelium does not normally present mitoses, as the kidney, liver, and salivary glands, are rarely the seats of origin of carcinoma.

Of the influences capable of causing epithelial metastases, trauma should be first mentioned. It is also very probable that traumatic influences have much to do with causing the cell-separations which give rise to many of the other tumors. In carcinoma, the changes in the subepithelial connective tissue play an important *rôle*.

Ribbert has already written upon the etiology of carcinoma.[1] The theory that carcinoma is due to an increased growth-energy of the epithelium, or to a diminution of the resisting capacity of the

[1] Virchow's Archiv, Band CXXXV; Münchener medicinische Wochenschrif, 1894, No. 17; Centralblatt für pathologische Anatomie, 1894, S. 697.

connective tissue, or both conditions combined, he regards as untenable. A correct conclusion can be reached only by studying the earliest stages of growth. In such observations he has found that the first changes are not a penetration of the epithelial cells into the connective tissue, but that the first thing observed is an active increase of the cellular elements of the subepithelial connective tissue. This causes a lifting up of the epithelial layer, which becomes irregular and convoluted. This seems to have little to do with the process that follows. The increased connective tissue grows up among the epithelial cells and causes irregular separations of the cells from their normal relations so that they become divided into groups and islands surrounded by the new connective tissue. This process does not interfere with the nourishment of the cells, but leaves them in condition to continue to proliferate. As they are now disconnected from the superficial cells, they cannot proliferate upward, and so must grow where the connective-tissue cells will allow. They proceed in the direction of the least resistance,—namely, into the intercellular spaces and lymph-canals, and in this manner the carcinoma develops. It is probably that, by virtue of the inflammatory state of the connective tissue with its accompanying hyperæmia, the epithelium has an increased growth capacity.

Ribbert has again had an opportunity recently to examine a carcinoma in its earliest stages. It developed from a psoriasis linguæ and presented small alveolæ in the subepithelial connective tissue. In this case, also, the growth of connective tissue among the epithelial cells was present; but it seemed to illustrate another *modus* of epithelial cell separation. The lower ends of the epithelial strings were separated from the rest of the cells either by the upward tension of the tissues or by virtue of the connective-tissue cells growing in between.

These observations hold good only for carcinoma springing from the flat epithelial cells. Ribbert has studied a carcinoma of the stomach, and found analogous conditions. The mucous membrane was thickened by an increase in the connective tissue and lengthening of

the gland follicles. In many places within the thickened area the glands were split up by the infiltration of connective tissue into small groups or single cells. The connective-tissue growth had broken through in many places into the muscularis mucosæ, and contained here and there collections of epithelial cells. This tissue did not anywhere extend deeply beneath the muscularis mucosæ, or even into the deeper layers of the mucosa. Nowhere did it penetrate the true muscular layer of the stomach. The impression given by this picture was that the gland epithelium had been separated by the growth of connective tissue, and that these by further proliferation pressed on down into the deeper connective tissue.

From these observations it would seem possible that epithelial separations may occur in the adult, and that normal epithelium, possibly only under the influence of long-continued inflammation, may thus originate carcinoma. It is not difficult to apply these ideas to all of the different varieties of carcinoma. It is a question whether the branchial carcinomata originate directly from a growth of epithelial remains in the fœtal clefts or develop secondarily from epithelium which has become separated by connective-tissue growth from its connections in a congenital fistula or cyst. The same thoughts apply to the origin of carcinoma from fœtal cysts. The same holds true of the origin of carcinoma from dermoid cysts, adenomata, and the paradental epithelial deposits of Malassez.

Bits of suprarenal capsule have been found embedded in the kidney, and these have sometimes been the origin of kidney tumors. It is not necessary that every bit of such separated tissue shall develop into a malignant tumor; often they remain unchanged or simply form adenomata. Tumors arise, then, by virtue of the separation of cells or groups of cells from their anatomical connections and their then assuming an independent growth. Dr. Ricker has made some valuable histological observations in the study of separations from the suprarenal bodies. He found a case in which a small mass of suprarenal capsule tissue was separated from the kidney tissue, but partially by a connective-tissue capsule. In one place this capsule was not

present, and here lay a number of small collections of suprarenal capsule cells in the kidney tissue between the uriniferous tubules. The connective-tissue substance of the kidney was but slightly increased, though in some places there was a considerable increase. Ribbert believes that from such separated cells a malignant tumor would develop.

As to the causes of the proliferation of the connective tissue which goes on to the formation of epithelial metastases, they must be very various. In some of the cases, as Ribbert has shown,[1] a subepithelial tuberculosis, especially that form designated as lupus, can be regarded as the cause. In such tissue carcinoma develops not infrequently. Of course the necessary inflammation can be caused by other micro-organisms, and possibly by the protozoa; though the identification of the latter has not yet been accomplished.[2]

It is not necessary that the inflammation be of parasitic origin. It can be caused in many other ways, as has long been known. As examples are the "parafin-," "tar-," and "chimney-sweep's cancer," the occurrence of carcinoma in scars, sequestrum cavities, on suppurating surfaces, in the gall-bladder in cases of gall-stones, in the digestive tract of alcoholics, in ulcers of the stomach, in seborrhœa of the skin, and psoriasis of the mucous membrane of the mouth. Many more such examples might be cited.

From the above observations the following may be deduced as to the abundant proofs of the origin of tumors.

Tumors originate before and after birth from a partial or complete separation of cells or groups of cells from their organic connections. The separated cells, no longer subject to the restraining influence of their normal connections, and still receiving an adequate nourishment, grow, and form tumors which, according to the size and organization of the separated mass, correspond in general structure with the organ from which they sprung, sometimes more, sometimes less. There is no essential difference between tumors of intra-uterine

[1] Münchener medicinische Wochenschrift, 1894, No. 17.

[2] Deutsche medicinische Wochenschrift, 1894, No. 15.

origin and those which develop after birth. Carcinoma originates from epithelial cells, which become separated in the epidermis, in the mucous membrane, or in glands, by the ingrowths of connective tissue, and thus become deposited in the same.

Ribbert's observations are important because of their bearing upon the origin of tumors in adults, and explain what the theory of Cohnheim has always failed to make clear. Ribbert's theory of the origin of carcinoma does not necessitate the existence and lying-dormant of carcinomatous cells for forty years, but explains how that diseased or normal epithelial cells may become tilted out of place by trauma, inflammation, or other causes, and continue to grow surrounded by connective tissue and in easy access to the lymphatic channels. It may be regarded as a continuation and elaboration of the principles of Cohnheim.

JAMES P. WARBASSE.